Ack. 11/13/72

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022

Application for Research Grant

RECEIVED
NOV 13 1972

Date: October 20, 1972

1. Name of Investigator(s): (include Title and Degrees) Leonide Goldstein, D. Sc. Associate Professor of Psychiatry. NJ College of Medicine and Dentistry. New Brunswick, N.J. Judith M. Nelsen, Ph. D. Post-Doctoral Fellow, same address.
2. Institution & Address: Institute for Mental Health Sciences. CMDNJ. Rutgers Medical School. P.O. Box 101. Piscataway, N.J. 08854.

3. Short Title of Project: Behavioral and electrophysiological effects of the "chronic nicotine state" in rats.

4. Proposed Starting Date: January 1, 1973

5. Anticipated Duration of this Specific Study: 2 years

6. Brief Descripton of Objectives or Specific Aims: See attached pages.

1003538866

7. Give a Brief Statement of your Working Hypothesis: Chronic nicotine treatment produces changes in the balance between reticular formation and limbic system arousal, enhencing "motivational" arousal and reducing "drive arousal".

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

8. Details of Experimental Design and Procedures: (Attach Separate Pages)

See attached pages

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location) The Laboratory at the Institute for Mental Health Sciences is comprized of 2 rooms, one 10'x20' and one 20'20'. We will have available all the equipment presently at the N.J. Neuropsychiatric Institute, including the items bought on the funds provided by the Council. A complete set up for animal care & maintenance will be provided.

10. Additional Requirements:

The only additional requirement will be for the purchase of a constant current stimulator needed for the experiments in which the RF will be directly stimulated.

11. Biographical sketches of all principal and professional personnel (append) See attached lists

12. List of publications: (Five most recent as pertinent) (append) See attached list

10035388862

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

13. Budget (1st year)

A. Salaries (Personnel by names) (16.66% Fringe benefits)	% time	Amount
Professional		
Judith M. Nelsen, Ph. D.	100	R
Leonide Goldstein, D. Sc.	10	----
Technical		
Katheleen Pelley, B.A.	100	R
Sub-Total		R
B. Consumable Supplies (list by categories)		
Animals		200.00
Food		200.00
Maintenance		100.00
Drugs, chemicals, EEG paper, electrodes		200.00
Sub-Total		700.00
C. Other Expenses (itemize)		
Travel. Principal investigator. 2 Meetings		400.00
Publications. Reprints		250.00
Sub-Total		650.00
D. Permanent Equipment (itemize)		
Constant voltage stimulator. Model 7151 Nuclear Chicago		1,000.00
		1,000.00
E. Overhead (15% of A+B+C)		~~3,597.30~~
Total		28,579.30

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	R	500.00	600.00		3,726	28,726
Year 3						

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature Leonide Goldstein, D. Sc
Director of Project

Telephone

Signature
Business Officer of the Institution

Telephone

10035888

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

Current

Title of Project	Source	Amount	Duration
Effects of microwave radiations on the EEG	US Navy Air-Development Center Warminster, Pa	25,000.00	1 year
Effects of a Prostaglandin analog on the EEG and behavior	Office of Naval Research. Arlington Va.	20,000.00	1 year

Pending

Effects of a Prostaglandin analog on the EEG and behavior	Office of Naval Research.	20,000.00	1 year

1003538869

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

Application for Research Grant. Item No 6

We reported previously, on the basis of studies carried under Grants from the Council for Tobacco Research-USA, that following chronic nicotine treatment there occurs in rabbits changes in certain features of the electrophysiological mechanisms of arousal. These changes have been interpreted as indicating a shift from the "classical" arousal mechanism (involving chiefly the mesencephalic reticular formation (RF)) to a qualitatively different arousal mediated by the limbic system. A proposed consequence of such an electrophysiological change was that behavior should become more specifically goal-oriented since, as Routtenberg pointed out (Psychol. Rev. 75, 51-80, 1968), the main feature of limbic system arousal is "incentive-oriented" while that of the RF is "drive oriented".

Working under subsequent Grants from the Council, we tested this proposal in an attention task in rats. We found that indeed chronic nicotine treatment did improve the efficiency of responses to goal-oriented stimuli without causing or be accompanied by a general increase in the behavioral levels of activity.

The results obtained in these studies invite further research directed both towards a better understanding of the mechanisms involved in arousal and of the motivation accounting for the widespread self-administration of nicotine by humans.

If as Routtenberg has suggested (and our present results imply) there exists a balance between the limbic and RF influences on arousal, it would follow that modification of the relationships toward greater limbic system control (resulting from chronic nicotine treatment) should alter the sensitivity of the RF arousal pathway to manipulation. This hypothesis can be tested by direct electrophysiological and pharmacological means. It is known that electrical stimulation of the RF produces cortical activation and that the current needed to elicit the response varies with the state of the brain. We propose to study the threshold for and duration of cortical activation in chronically saline-treated and nicotine-treated rats. It is also known that a number of stimulant and psychoactive drugs exert their effects by acting promarily at the level of the RF. One would expect a comparable change in the efficacy of such drugs following chronic nicotine treatment. The drugs of particular interest would be: D-amphetamine, methyl-phenidate, physostigmine (following protection of the periphery with methyl-atropine), LSD-25, and, in view of the present controversy concerning classification of the nature of the effect, delta-9 THC.

1003538870

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

Besides the study of direct electrophysiological effects at cortical and subcortical levels, we intend to conduct parallel behavioral studies. These would be focused on the elucidation of the functional consequences of the electrophysiological and pharmacological manipulations. The Continuous Attention Task appears well-suited for such studies since it has been demonstrated to be sensitive to both the level and qualitative nature of arousal.

10035382

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

Application for Research Grant. Leonide Goldstein.

Item 8.

Two related lines of investigation are planned. The first concerns electroencephalographic measures of cortical activation induced by electrical stimulation via the mesencephalic reticular formation (RF) arousal pathway and by pharmacological agents. In previous applications for "Research Grants" from the Council (dated November 25, 1970 and October 25, 1971), we have reviewed the surgical and EEG measurement technics which we have developed for application to such studies. We propose to prepare with cortical and subcortical (RF) electrodes an experimental group of approximately 20 rats (Holtzman, Sprague-Dawley, male). These animals will undergo adaptation training in an EEG recording chamber. They will then be assigned in random fashion to two groups, one of which will receive chronic treatment with nicotine (100 ug/kg, s.c., t.i.d.) and the other, with physiological saline.

A schedule for delivery of small doses of electrical stimulation to the RF will be carried out to determine the threshold for and the duration of cortical activation resulting from direct stimulation of the RF arousal pathway under conditions of chronic nicotine and chronic saline treatment. Arousal (desynchronization) will be measured and quantified from the cortical EEG recordings. Further, comparisons between the cortical effects of D-amphetamine, L.S.D., physostigmine, and tetrahydrocannabinol in animals treated chronically with either nicotine or saline will be made.

Electrical current will be delivered by a Nuclear-Chicago constant current stimulator. Parameters of the current will be within a moderate range which has been shown to cause only reversible effects both on behavior

1003538872

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

and neural tissue (Kornetsky and Eliasson, 1969; Nelsen, 1970).

The second area of investigation involves behavioral measures of the effects of modifications in the proposed balance between limbic and RF control of arousal. Because in our hands it has proven to be impressively sensitive to levels of arousal, the same form of the behavioral task of Kornetsky and Eliasson (1969) which we have described in previous grant applications to the Council (dated November 25, 1970 and October 25, 1971) will be used to assess the functional consequences of electrical and pharmacological manipulations of the RF arousal pathway.

Twelve rats will be prepared surgically with electrodes at the sensory-motor cortex and in the mesencephalic RF. Following recovery (about three weeks), these animals will be trained to perform on the visual attention task. The rats will be partially food deprived and maintained at approximately 85% of their normal, free-feeding body weights. They will be trained to press a lever for a food pellet reinforcement following the presentation of a conditional stimulus (C.S.) which is the white cue light in a standard operant conditioning box. Training is carried out in a series of phases such that initially the task is quite elementary, i.e., continuous reinforcement or fixed ratio 1 in the presence of a constant C.S. During successive training sessions, an inter-trial interval (I.T.I.) is introduced and the duration of the C.S. is reduced in step-wise fashion while a punishment contingency for inappropriate responding is also added. In the task's final form, the duration of the cue light is only 0.2 sec, followed by an available response time of 5.0 sec during which only the first lever press

10035388873

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

is reinforced. Failure to press after a C.S. is scored as an omission error (o.e.) and has no consequence for the animal other than the loss of a reinforcement pellet. The I.T.I. is variable (so that the rat is not learning to time responses according to a fixed interval) with a mean of 10.0sec. A lever press during the I.T.I. is scored as a commission error (c.e.) and is punished by the imposition of a 30.0 sec "time-out". Additional responses during the time-out reset the punishment clock to 30.0 sec and are also scored as c.e.'s. A session is terminated after 100 reinforcementshave been delivered or after one hour has elapsed. The task is programmed via electro-mechanical modules.

This type of task in which the animal is asked not only to make appropriate responses but also to inhibit inappropriate responses is difficult for rats to learn and requires several months of training to achieve efficient performance which we have defined as: 1) for o.e.'s, #o.e./# reinforcements times 100 $\leq$ 30%, and 2) for c.e.'s, #c.e./# reinforcements times 100 $\leq$ 30%. After the rats have reached criterion levels of performance, half the group will be subjected to chronic treatment with nicotine (100 ug/kg, s.c., t.i.d.) and half to physiological saline. After approximately one week of regular injections, a schedule of low current level electrical stimulation to the RF will be introduced during the testing sessions. Such stimulation has been shown to disrupt performance in a similar task (Kornetsky and Eliasson, 1969) where electric foot-shock was the reinforcing agent. Since based on our previous work, differential baseline behavior is expected depending on whether rats are nicotine- or saline-treated, each group (in

1003538874

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

fact, each animal) will act as its own control. Our hypothesis is that because nicotine-treated rats are in a state of greater incentive-oriented arousal (hippocampal predominance in the control of cortical function), their performance will be affected less detrimentally by RF stimulation than the performance of saline-treated animals.

Further, behavioral studies are planned which will focus on the possible protective action of the chronic nicotine state on the disruptive effects of pharmacological agents known or suspected to act on the RF arousal pathway by causing a relative increase in general or drive-oriented arousal and hence, decrease in incentive-oriented arousal. These agents will include D-amphetamine, L.S.D., physostigmine, and tetrahydrocannabinol. They will be administered according to a randomized block design and the results will be tested by applying an analysis of variance.

Kornetsky, Conan and Elliasson, Mona: Reticular Stimulation and Chlorpromazine: An Animal Model for Schizophrenic Overarousal. Science 165: 1273-1274, 1969.

Nelsen, Judith M.: Single Dose Tolerance to Morphine Sulfate: Electroencephalographic Correlates in Central Motivational Systems. Unpublished Doctoral Dissertation. (Boston University) 1970.

1003538875

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

Bhattacharya, I.C. and Goldstein, L. Influence of acute and chronic nicotine administration on intra- and inter-structural relationships of the electrical activity in the rabbit brain. Neuropharmacol. 8, 109-118, 1970.

Greenberg, R.S. and Goldstein, L. An EEG study of the relationships between brain structures in rabbits under ethanol and d-amphetamine. Quart. J. Studies Alcohol. 30, 843-848, 1969.

Goldstein, L., and Dolge, G. An analysis of the effects of ethanol on cortical and subcortical electrical activity in cats and rabbits. in: Interm. Symposium Biological Aspects of Alcohol Consumption. O. Forsander and R. Erikson, ed. Finnish Foundation for Alcohol Studies, 20, 267-274, 1972.

Nelsen, J.M., and Goldstein, L. Improvement of performance on an attention task with chronic nicotine treatment in rats. Psychopharmacologia, 26, 347-360, 1972.

Nelsen, J.M., and Goldstein, L. Chronic nicotine treatment: acquisition and performance of an attention task by rats. Submitted for publication: Neuropharmacology, 1972.

1003538826

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

R: REDACTED MATERIAL

Curriculum Vitae

Leonide Goldstein, D.Sc.

Born: R

Permanent Residence in the United States - Alien registration No. REDACTED

Marital Status: REDACTED

REDACTED	Student at the Conservatoire National de Musique, Paris
	Graduated in violin, harmony and composition.
	Military duty, French Army
	Technical Assistant Institut de Biologie, Paris
	Research Assistant
	Non-commissioned Officer, French Army
	Undergraduate studies University of Paris
	Research Associate Laboratoire de Physiologie School of Medicine, University of Montpellier, France
	Member of the Research Division of the Free French Forces
	Special assistant to Dr. H. J. Muller, Amherst College, Amherst, Mass.
	B.A. and M.A. Amherst College
1945-47	Assistant Professor University of Paris (Physiology & Genetics)
1947-53	Acting Director Laboratoire de Biometrie of the French National Research Council
1951	Doctor of Sciences degree. University of Paris, Sorbonne
1953-58	Assistant Professor, Neurophysiology, Ecole Pratique des Hautes Etudes, Sorbonne
1958-61	Associate Professor, Pharmacology, Emory Univ., Atlanta, Georgia
1961-64	Neuropharmacologist, Bureau of Research, Neuropharmacology Section, N. J. Neuropsychiatric Institute, Princeton, N. J.
1964	Research Scientist Grade 1, Bureau of Research, Neuropharmacology Section, N. J. Neuropsychiatric Institute, Princeton, N. J.
1966	Consultant - McNeil Laboratories, Fort Washington, Pa.
1969	Visiting Senior Fellow - Department of Biology - Princeton University
1972	Associate Professor of Psychiatry. Rutgers Medical School.

Membership in Scientific Societies:

REDACTED REDACTED

Honors:

Croix de Guerre (1939-40): Medal of the Free French Forces: Palmes Academiques (1950). Associate Editor "The Journal for the Study of Consciousness" and "Research Communications in Chemical Pathology and Pharmacology".
President - French Club of Princeton (1969-1971).
Trustee - Schizophrenia Foundation of New Jersey (1972).

Listings:

American Men at Science - Who is Who in the East.

Publications:

Author or co-author of 140 papers and abstracts dealing with genetics, endocrinology, electro-physiology and pharmacology of the brain.

(Revised February 1972)

100353887

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

R: REDACTED MATERIAL

CURRICULUM VITAE

Judith M. Nelsen, Ph.D.

BORN: R - Milwaukee, Wisconsin, U.S.A.

MARITAL STATUS: REDACTED

Primary and secondary studies, public schools of Town of Lake and City of Cudahy, Wisconsin

Undergraduate studies, University of Wisconsin-Milwaukee (Letters and Science, Pharmacy)

Laboratory assistantship in bacteriology (University of Wisconsin-Milwaukee)

Undergraduate studies, University of Wisconsin- Madison (Pharmacy, Psychology)

REDACTED

Research assistantship in physical chemistry (University of Wisconsin-Madison)

Summer research assistantship in physical chemistry (from the U.S. Department of the Army at the University of Wisconsin-Madison)

B.S.(HONORS) degree. University of Wisconsin. Madison, Wisconsin

Graduate studies, Boston University School of Medicine, Division of Medical Sciences, Department of Pharmacology an Experimental Therapeutics (Major professor: Conan Kornetsky, Ph.D., Director, Laboratory of Behavioral Pharmacology)

Graduate School Research Fellowship

1966-70 Public Health Service Research Fellowships (N.I.M.H.)

1970 Doctor of Philosophy degree. Boston University. Boston, Mass.

1970-72 Post-doctoral appointment. N.J. Bureau of Research in Neurology and Psychiatry. Box 1000, Princeton, N.J.

1973 Senior Scientist. Rutgers Medical School. Department of Psychiatry, Piscataway, N.J.

10035388 28

HONORS: Sophomore Honors (U.W.); Senior Honors (U.W.); Sigma Epsilon Sigma (U.W.); Rho Chi (U.W.); Phi Kappa Phi (U.W.); Sigma Xi (B.U.)

PROFESSIONAL SOCIETY MEMBERSHIPS: REDACTED

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000

PUBLICATIONS

Nelsen, Judith M. and Conan Kornetsky: Single Dose Tolerance to Morphine Sulfate: EEG Changes. The Pharmacologist 10: No.2, 1968.

Weil, Andrew T., Norman E. Zinberg, and Judith M. Nelsen: Clinical and Psychological Effects of Marihuana in Man. Science 162: 1234-1242, 1968.

Nelsen, Judith M. and Leonide Goldstein: Improvement of Performance on an Attention Task with Chronic Nicotine Treatment in Rats. The Pharmacologist 13: No. 2, 1971.

Nelsen, Judith M. and Leonide Goldstein: Improvement of Performance on an Attention Task with Chronic Nicotine Treatment in Rats. Psychopharmacologia 26: 347-360, 1972.

Nelsen, Judith M. and Conan Kornetsky: Morphine-Induced EEG Changes in Central Motivational Systems: Evidence for Single-Dose Tolerance. Fifth International Congress on Pharmacology (Abstracts, p. 166, #993), 1972.

Goldstein, Leonide and Judith M. Nelsen: Some Views on the Neurophysiological and Neuropharmacological Mechanisms of Storage and Retrieval of Information. Merck Symposium on Memory, Transfer of Information (H. P. Zippel, ed.),1972 (In press).

Nelsen, Judith M. and Conan Kornetsky: Single Dose Tolerance to Morphine Sulfate: Quantitative Electroencephalographic Amplitude Correlates in Central Motivational Systems. Submitted for publication in J. Pharmacol. Exp. Ther., 1972.

Nelsen, Judith M. and Leonide Goldstein: Chronic Nicotine Treatment: Acquisition and Performance of an Attention Task by Rats. Submitted for publication in Neuropharmacology, 1972.

10035388?9

Source: https://www.industrydocuments.ucsf.edu/docs/zryl0000